International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2021; 9(4): 10-18
Received: 07-05-2021
Accepted: 09-06-2021

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Bacopa monnieri (Brahmi): A potential treatment course for neurological disorders: Review

Prachi Kulkarni

Abstract
Ayurvedic medications are increasing rapidly due to its safety profile because though it heals slowly, but it cures completely. Various studies conducted on *Bacopa monnieri* have shown that it increases signaling molecules involved in the process of synaptogenesis. Also, when it is combined with cognitive stimulation, it can enhance long-term potentiation (LTP) and also improves cognition in older adults leading to a positive effect on a neurodegenerative disease. This review focuses on effect of Medhya rasayana (extracted from *Bacopa monnieri*) on neurodegenerative disorders.
Evidence shows presence of various mechanisms by which this herb is known to enhance memory and learning skills. *Bacopa monnieri* has shown alteration of potential attenuation of Dementia in Alzheimer's revealing its medicinal properties.
Ayurvedic medications have shown potential long term effects with minimal or no side effects. Antioxidant properties of *Bacopa monnieri* extracts have shown positive effect on mental function. Medicinal properties of *Bacopa monnieri* extracts can be used to reduce the onset of Alzheimer's and also to treat various neurological disorders. Therefore, more research on humans has to be conducted in order to understand the mechanism of action in a better way.

Keywords: *Bacopa monnieri*, medharasayana, neurodegenerative diseases, neuroinflammation, schizophrenia, signaling pathway

1. Introduction
Bacopa monnieri also known as Brahmi is a creeping, perennial herb originated from wetlands of Eastern, Southern India, Africa, Australia, Asia, Europe and South and North America. It'sa herb utilized in Ayurveda [1]. The US Food and Drug Administration (FDA) has warned manufacturers of dietary supplement products that contain *Bacopa monnieri* against making illegal and unproven claims that the herb can treat various diseases. It belongs to the family Scrophulariacae and it is classified as "medhyarasayan", a drug that is used to improve memory and interact [3]. It has been tested in various animal models to understand its effect on memory, anti-inflammatory response, antiamnesic activity, etc. *Bacopa monnieri* is the main constituent in preparation of various Ayurvedic medicines that are often prescribed for cognitive dysfunction. It is said to improve memory functioning in neurodegenerative diseases [4].
Group of medical conditions that affect neurons primarily in the brain of a human are called neurodegenerative disorders. The building units of the central and peripheral nervous system that includes the brain and spinal cord are known as neurons. Neurons don't reproduce or replace themselves, instead when they become damaged or die they cannot be replaced by the body. Huntington's, Alzheimer's, and Parkinson's disease are few examples of Neurodegenerative disorders. Some of the Neurological conditions are incurable and enervating leading to progressive degeneration of nerve cells and / or death of nerve cells. This further causes problems with movement (called ataxias), or mental functioning (called dementias) [6]. To treat these diseases, various phytochemical extracts can be used. Other than Brahmi some of them are:

1.1 Ashwagandha
Indian Ginseng or *Withania somnifera*, fam. Solanaceae, is a common ayurvedic herb used as anti-stress agent or as an adaptogen. The root of Ashwagandha contains variety of compounds *viz*. 40 withanolides, 12 alkaloids and several different flavonoids and sitoindosides [8]. The mechanism it exhibits at molecular level is that it can inhibit activation of NF-κB, blocking production of β-amyloid (Aβ), reduces cell death by apoptosis, restores synaptic function and enhances antioxidant effects via the migration of NRf2 to the nucleus, playing major role in increasing the expression of antioxidant enzymes [8].

Treatment studies of human neuroblastoma cell line (SK-N-SH) along with methanolic extracts of Ashwagandha root will emanate dendrite extension, synapse formation and neurite growth [8]. Also, Ashwagandha root constituents have more beneficial effects in neurodegenerative diseases may be because of their antioxidant, antiapoplytic, anti-inflammatory and antiaxiolytic activities. They tend to enhance mitochondrial dysfunction and restore energy levels and increased antioxidant levels such as reduced glutathione [8].
However, the life span of Ashwagandha in brain and circulation is yet not known. Clinical trials of Ashwagandha in dementia patients have not been performed. Although a preliminary study has shown that *Withania somnifera* (500mg/day) added concomitantly to medications amplifies reaction time, auditory-verbal working memory and social cognition in patients suffering from bipolar disorders [13].

1.2 Turmeric

Diferuloylmethane (bis-α,-unsaturated β-diketone) or Curcumin, derived from the rhizome of *Curcoma longa*, fam. Zingiberaceae, plays important role in anti-inflammatory, antioxidant and cancer chemopreventive properties [14]. At molecular level, it has shown reduction in expression of glial fibrillary acidic protein (GFAP), enhanced spatial memory in Aβ-induced AD model of rat, and declined COX-2 and GFAP expression in Aβ-treated astrocytes [15]. *In vitro* and *in vivo* studies have shown that curcumintethers A$\beta$and suppress its aggregation and also oligomer and fibril formation [16]. *In vivo* studies on transgenic mice have shown that dietary curcumin not only crosses blood brain barrier decreasing deposition of Aβ but also suppresses phosphorylation of Tau protein [17].
The shelf-life of curcumin in brain and circulation is yet not known. Although number of small studies in healthy individuals have been conducted but has not been performed in dementia patients. A study conducted in healthy adults over the age of 60 years, Curcumin (400 mg/day) remarkably enhances performance on working memory tasks and sustained attention when compared to placebo [18]. Another study suggests that treatment along with curcumin (1500 mg/day) showed no loss of cognition in treatment group as compared to placebo group where loss of cognition was reported among community-dwelling older adults [19].
Recently, *Bacopa monnieri* has been discovered as another ayurvedic medication that has shown positive effects in the decrease of neurodegenerative disorders. Various studies reveal its major role as reduction of lipoxygenase activity reducing lipid peroxidation, chelates ion and also known to increase glutathione peroxidases. It is also known to protect cholinergic neurons which in turn reduce anticholinesterase activity when compared to other classes of drugs such as donezepil and galantamine. It is usually known to protect the hippocampus, striatum and cells present in the prefrontal cortex against cytotoxicity caused during neurodegenerative diseases. The effects of *Bacopa monnieri* have been studied in various experimental models such as rats and mice and the results concluded with no side effects [1]. Such revelations have led to the current review which summaries the effect of *Bacopa monnieri* in diseases like Alzheimer's, ADHD, schizophrenia and Neuroinflammation.

2. Brahmi extraction methods

Various studies are reported on extracts of bioactive compounds in leaf extract of *Bacopa monnieri*. The ethanolic extract of *Bacopa monnieri* includes alkaloids (nicotine, brahmine, and herpestine), sterols like b-sitosterol, stigma sterol, d-mannitol, acid A. The major contributors of *Bacopa monnieri* are triterpenesaponins of the class dammarane, they are named as bacosides and bacosaponins [4]. Bacoside A is mixture of three compounds A2, A2' and A3 and bacosideB.

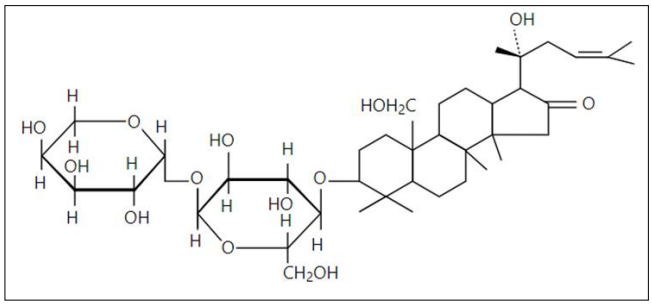

Fig 1: Chemical structure of Bacoside [1]

A fraction which is used as a standard i.e., no less than 60% of bacoside A extract was used to examine learning, memory, and behavior. CDRI 08 extract of *Bacopa monnieri* was standardized to contain not less than 55% of Bacosides. This plant is harvested twice a year by hand. The active component of *Bacopa monnieri* is analyzed through spectrophotometry and high performance liquid chromatography. The whole dried plant is extracted with ethanol, which produces CDRI 08, a standardized component for active compounds [20].
Similarly, for methanolic extracts of *Bacopa monnieri*, powdered material is to be soaked with methanol at room temperature for 3 days and the mixture is to stir continuously with sterile glass rod. Filtering of the mixture with the help of Whatman paper and removal of the solvent by rotatory evaporator has to be performed. The crude extract of methanolic components of *Bacopa monnieri* was used to study anti-depressant like effects in mice [21]. Another method for extracting bacoside rich extract from leaf is by drying the extract in hot air oven at 37 to 42 degree Celsius. The dried herb is powdered and sieved properly such that, the size obtained is around 30-40 mesh. In soxlhet extractor the herb is defatted with hexane and then it is further treated with acetone and methanol such that, the obtained mixture of herb contains bacosides.
This is then concentrated to 1/20thpart and precipitation of bacosides is obtained in acetone, which is filtered to get crude bacoside content. This crude is dissolved into 2-10parts of water, n –butanol is used to extract bacoside solution. As it is concentrated under volume, semi-dry mass is obtained. This is further processed by adding and stirring 1-5% cyclodextrin, to stabilize bacosides. By spray-drying the content at 90-110 degree Celsius, mixture obtained of Bacopamonnieri which is rich in bacosides [1].
Another method for *Bacopa monnieri* extraction was that the standard tablet formulation that comprised of either 300 or 600 mg of prepared dried *Bacopa monnieri* extract. The aerial part of *Bacopa monnieri* was collected and cut into pieces, which was then dried in hot-air oven at 50 degree Celsius and then it was crushed. This powder was then allowed to percolate for around 8h with 95% ethanol for three times and then it was filtered. The total saponin content was determined using HPLC apparatus which consisted of mixture of bacoside A3, bacopside II, Bacopasaponin C, and Bacopaside I. This prepared tablet was given to healthy elderly volunteers to determine function of both cholinergic and monoaminergic systems [22].

3. Effect of *Bacopa monnieri* (Brahmi) on various neurological disorders

3.1 Alzheimer's disease

Alzheimer disease is neurodegenerative disorder that is characterized by memory loss, erratic behaviour and memory loss. Although, medications for Alzheimer have shown limited effectiveness, yet no cure exists for Alzheimer's till date. Peptide Aβ plays a vital role in AD toxicity and progression, as it assembles into insoluble amyloid fibrils that accumulates in extracellular neuritic or senile plaques [23]. This is followed by dementia, cognitive declination, neuronal deterioration and synaptic dysfunction [27].

Due to unsaturated fatty acids in cell membrane, higher metabolic rate and lower activity of antioxidants including catalase (CAT) and glutathione peroxidase (GPx), and cytotoxic actions of glutamate, brain is particularly susceptible to free radical damage. Body produces various free radical scavenge mechanisms namely enzymatic or non-enzymatic. Enzymatic are the ones that includes CAT, superoxide dismutase (SOD), glutathione reductase which acts as first line of defence when encountered by ROS. Non-enzymatic which includes selenium, Vitamins (A, E, C), glutathione (GSH) and coenzyme Q10 whose antioxidant actions protects neuronal tissue from damage of free radicals. However, imbalance that occurs between protective antioxidant mechanisms and free radical species is vital for free radical damage in older population that ultimately results in cognitive decline and aging [1].

Major role of *Bacopa monnieri* extract as an antioxidant is mainly due to its effect on enhanced concentrations of Glutathione (GSH) and various enzymatic antioxidants like CAT, GPx and SOD and also as free radical scavenging agent (Figure 2). Therefore, administration of Brahmi in certain indicated doses may act as remedy for age-associated memory and cognitive decline seen in Alzheimer's Disease [1].

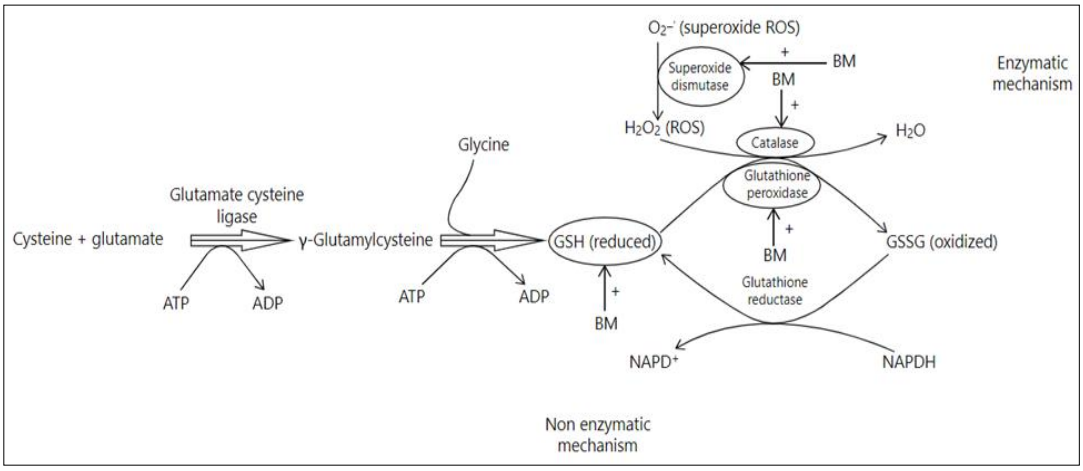

Fig 2: Enzymatic and non-enzymatic mechanisms of EBm [1].

Another study indicates, when Bacoside A (*Bacopa monnieri* compound) with Aβ42 was pre-incubated in SH-SY5Y cell line model, a significant inhibitory effect of fibrillation, cytotoxicity and membrane interactions of beta-amyloid (1-42) were observed. As Aβ plaques can be toxic to synapses and neuronal cells, hence, inhibition of Aβ aggregates and its assembly are considered one of the major and primary therapeutic strategies in AD treatment and its subsequent prevention. Aβ42 monomer initially generates oligomeric species that are cytotoxic and membrane-active, which then accumulates into fibrils, promoted through interactions via bilayer interface. Thus, Aβ42 aggregation was reduced and its membrane interaction was also inhibited when incubated with Bacoside A [23].

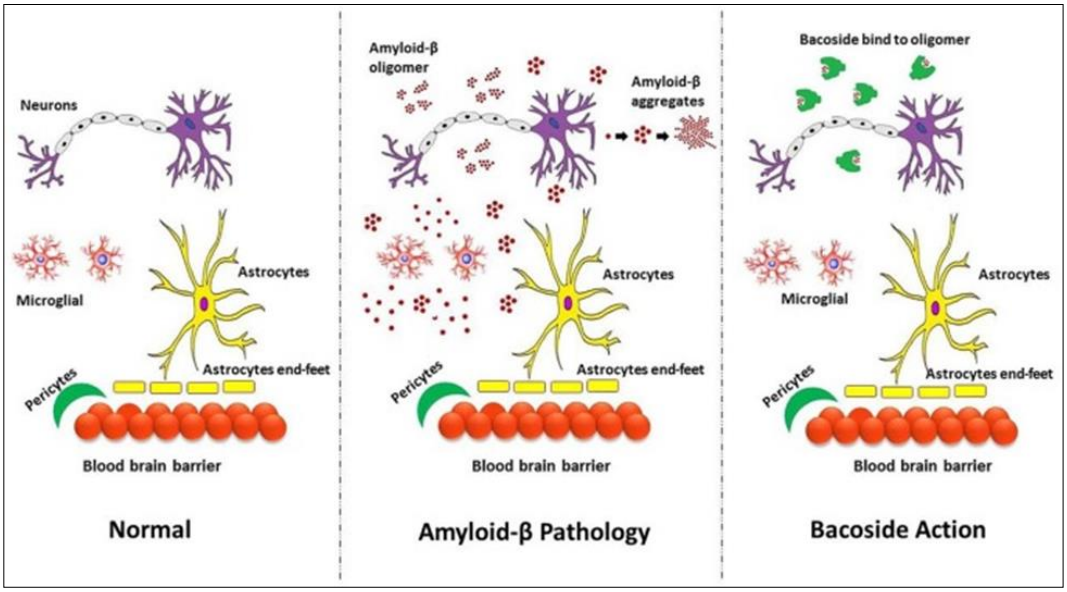

Fig 3: Mechanism of Action of Bacoside A in AD [23]

3.2 Schizophrenia

Schizophrenia is a neuropsychriatric disorder characterized by positive symtoms including hallucination, thought disorder, increased motor functions, perpetual disturbances and delusions while negative symptoms comprises of social withdrawal, avoliation, anhedonia and alogia and deficits in cognitive abilities [28].

Till date, for the management of Schizophrenia, antipsychotic treatments mainly Dopamine receptor subtype 2 (D2) antagonists, have proven beneficial in reduction of positive and negative effects but failed to be effective in relieving the cognitive deficits that are associated with the disease [31]. However, these antipsychotics often cause several adverse effects, such as Parkinsonism. Therefore, developing a novel medication for improving cognitive abilities with fewer adverse effects is important [28].

The exact mechanism of *Bacopa monnieri* is yet unknown, however cholinergic, anti-oxidant and adaptogenic effects are reported in preclinical trials on Central nervous System [33]. The effect of *Bacopa monnieri* along with an allopathic medicine olanzapine was used in management of Schizophrenia**.** Olanzapine is atypical antipsychotic drug that is generally used to treat Schizophrenia and Bipolar disorder. However, there was initial improvement in psychopathology with olanzapine. Also, there was positive symptom improvement which could be possibly due to delayed effect of drug olanzapine [34].

By enhancing kinase activity, restoration of synaptic activity and enhancing nerve impulse transmission in brain, *Bacopa monnieri* is reported to repair the damaged neurons. The nootropic effects of Brahmi can possibly mediated by its constituents *viz*. bacosides A and B via glutaminergic mechanism [35]. However, there is lack of literature to provide supporting data for therapeutic effect of Brahmi in Schizophrenia. The improvement due to Brahmi in positive symptoms and general psychopathology could be mediated via dopaminergic mechanisms and its enhancing properties. Although, further research is yet to be done to understand therapeutic effects of Brahmi in several dimensions of Schizophrenia and also, exploring the neurochemical and neurophysiological mechanisms behind the same [34].

3.3 Attention Deficit Hyperactivity Disorder

ADHD (Attention Deficit Hyperactivity Disorder) is a psychiatric developmental disorder that is classified with certain set of symptoms including hyperactivity, inattention, aggression and impulsivity in childhood. Stimulant medications regulate neurochemical deficiencies by increasing noradrenalin / norepinehrine (NA/NE) and catecholamine dopamine (DA) within the prefrontal cortex (PFC) region in the brain especially [20].

Modern treatment that is followed for ADHD includes psycho-stimulant drugs like tricyclic antidepressants (TCAs) *viz*. imipramine and tryptalline and methylphenidate /amphetamine. Side-effects of the drug methylphenidate are insomnia, anorexia and loose motions, while TCAs have known to cause anti-cholinergic side-effects including constipation, dry-mouth, increased appetite and weight gain [36].

From Ayurvedic perspective, ADHD is considered in terms of '*doṣaprādhanya'*, that can be suggested as *Vāta-pitta*. Aggravation of *vata* is considered responsible for hyperactivity and inattention. Whereas, aggravation of *pitta* leads to impulsivity. To confirm the selected dose and dosage regimen of *Brāhmīghṛtam,* pilot, exploratory study was conducted. To assess the symptoms of ADHD (also known as ADHD rating scale-IV), Dupaul ADHD rating scale was used [36]. It is user friendly and reliable for assessing response of the treatment and also for diagnosing ADHD in adolescents and children. According to the study, only 10 children completed the study and 5 children were dropped out of study either due to time constraints on parents for follow-up visit or due to vacation. Children were provided *Brāhmīghṛtam* for 2months of period and were asked to take approx. 10 ml(2 teaspoons) either with lukewarm water or with milk in morning between 7a.m to 8.am everyday, empty stomach. During this period of study, the children did not receive any other psychotherapy treatment. The parents were also instructed to bring children for follow-up visit after 15days of interval and at each visit, ADHD rating scale was re-administered [36].

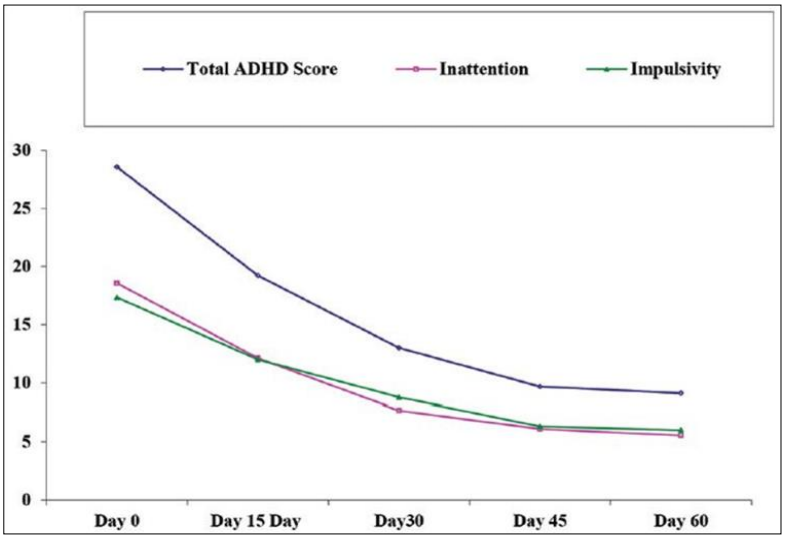

Fig 4: Brahmi effect on ADHD score [36]

The children at every visit were assessed with ADHD scale and the total score obtained was divided into two types *viz*. impulsivity and inattention subtypes. The results showed gradual decrement in total ADHD as well as in its components [36].

3.4 Neuroinflammation in Anxiety and Depression

Bacopa monnieri is also known for anti-inflammatory effects

on macrophages. When pathogens or inflammatory signals affect CNS, Microglia as a primary line of self-defense, migrate at the site of infection. When the microglia is activated it gets transformed into two phenotypes, either neurotoxic phenotype (M1) or neuroprotectivephenotype (M2). Microglia persist in two specific functional states *viz*. M1 phenotype which is responsible for production of proinflammatory cytokines like Interleukin 6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α). Second functional state is M2 phenotype which secretes inflammatory cytokines like IL-10 and down regulates the M1 response [38]. The imbalance between M1 and M2 subsets of microglia results in chronic inflammation. Under circumstances like disease or major injury, microglia ceases in M1 phenotype perpetuating inflammatory response. Due to this, there is upregulation of proinflammatory cytokines eventually leading to neuronal cell death (Figure 5).According to recent studies, this type of upregulation and activation is not only seen in neurodegenerative diseases but also in Schizophrenia, anxiety and depression [38].

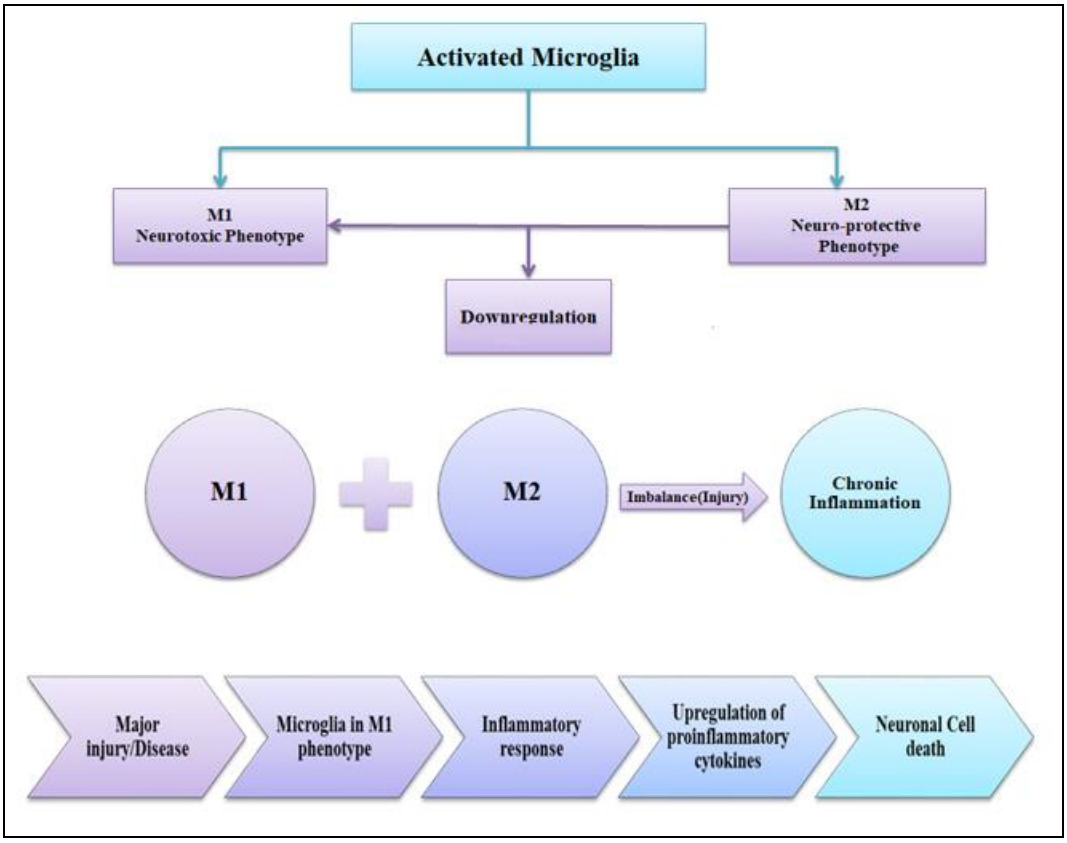

Fig 5: Graphical Representation of Neuroinflammation [38]

Bacopa monnieri inhibits release of IL-6 and TNF- alpha from monocytes that is stimulated with lipopolysaccharide [40]. However, it ameliorates M1 microglial response with reduction in release of TNF- alpha and IL-6 that leads to decrease in neuroinflammation. On the contrary, LPS-activated microglial cultures release small amount of IL-10 and *Bacopa monnieri* doesn't show any effect on this release [38]. Bacoside content from Bacopa is also known for activation of neurotransmitter such as acetylcholine, serotonin, GABA and glutamate. *Bacopa monnieri* is thought to increase concentration of 5-hydroxytryptamine in hippocampus, hypothalamus and cerebral cortex region of brain.

3.4 Learning memory

By BME treatment, balanced functions of neurotransmitters like serotonin (5-hydroxytryptamine, 5HT), acetylcholine (Ach), glutamate (Glu), catecholamine and*γ*-aminobutyric acid (GABA) were altered [4]. A study reported that BME treatment enhanced 5-HT level in hypothalamus, cerebral cortex and hippocampus [43] directly/indirectly the Ach concentration was also modified by other neurotransmitter systems. To understand the effect of BME treatment, the first step was to estimate level of neurotransmitters [44] and they found during postnatal period, BME treatment significantly up regulated the expression level of GABA, Glu, 5-HT and Ach. However, it decreased the expression levels of Dopamine (DA). Remarkably, the reported inhibitory effects of cholinesterase activity of BME might enhance Ach expression levels and increase memory [45]. On the other hand, the serotonin (5-HT) receptors present in GAB Aergic neuron might activate GAB Aergic neuron in turn increasing release of GABA. Although increased expression of GABA in hippocampus could lead to activation of inhibitory GABA receptors present on cholinergic systems leading to suppression of Ach release and 5-HT receptors might act directly on cholinergic system thereby enhancing the release of Ach [46]. The trends of 5-HT expression levels have drawn attention to study and analyze the effect of BME on 5-HT system. Studies designed to understand the pathway associated with 5-HT system has been shown in figure 6.

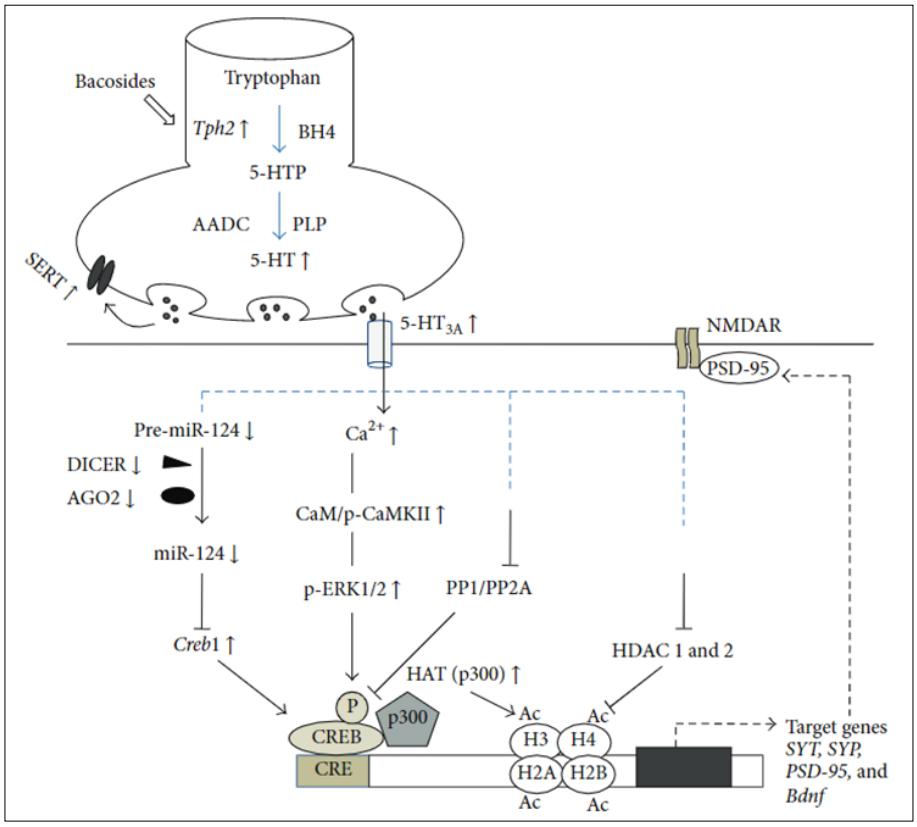

Fig 6: Mechanism of serotonin mediated signalling pathway that is activated by Bacopa during learning [4].

Additional beneficial applications of *Bacopa monnieri*

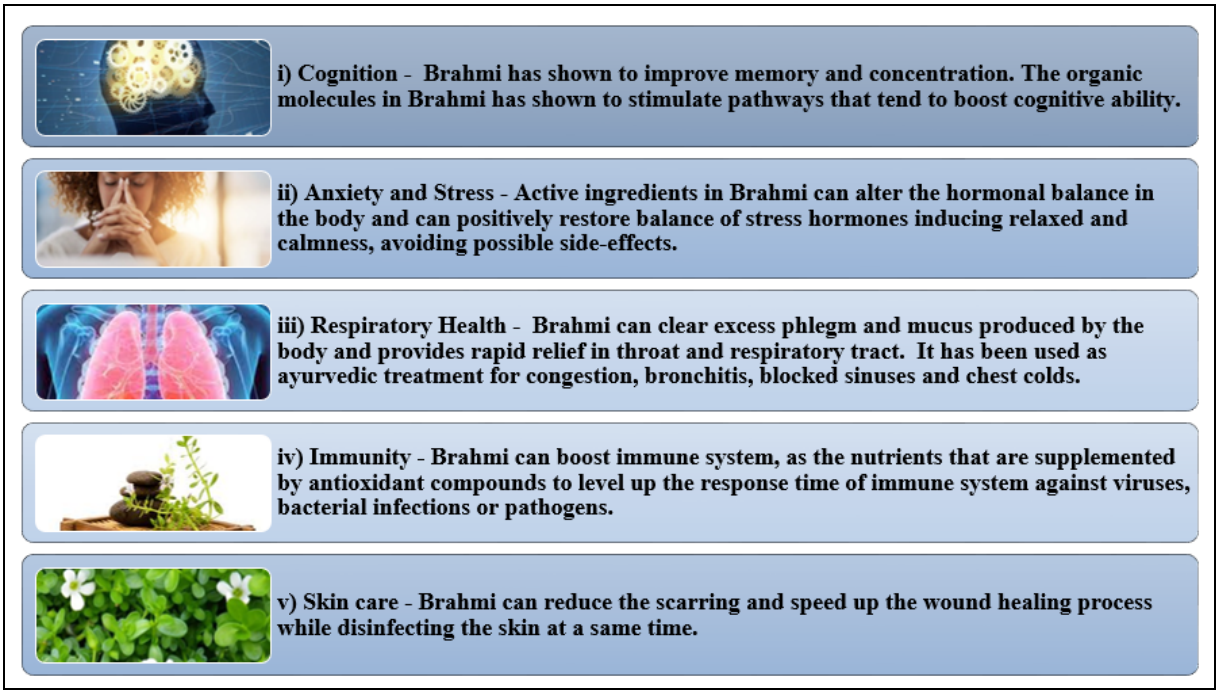

Fig 7: Applications of Brahmi [50]

4. Conclusions

This review article can be concluded based on experiments performed on animals strongly suggesting Brahmi as promising agent in AD and different forms of cognitive impairment [1]. Since *Bacopa monnieri* ameliorates inflammation, it can possibly be a link between systemic anti-inflammatory properties and its effect on mind which could possibly lay its ability to regulate neuroinflammation in CNS. *Bacopa monnieri* and its constituents play major role in development of novel therapeutics that can target neuroinflammation and treat CNS disorders like Alzheimer's disease, depression and schizophrenia [38]. Administration of *Bacopa monnieri* extract (300 mg) dose daily for 6 weeks produced significant effect on some component associated with memory [51]. However, long term study beyond 6 weeks is recommended to study analyze long term effect of this herb [51]. The effect of Brahmi along with olanzapine resulted in improvement of psychopathology in Schizophrenia. The

antioxidant properties in *Bacopa monnieri* led to positive effect on mental functions [34].

Bacopa monnieri can repress AChE activity which results in increased cholinergic function leading to increased working memory. Due to oxidative stress and cholinergic degeneration, resulting in mild cognitive impairment (MCI) and early phase Alzheimer's disease, plant extract of *Bacopa monnieri* can be beneficial [22]. Constituent of *Bacopa monnieri* extract, bacosides is known to enhance cognitive function by modulation of different transmitters [4]. Brahmi consumption in ADHD showed improvement in ADHD score (based on ADHD scale) while showed decrease in inattention symptoms [36].

There are still a lot of studies required in this field which needs to be directed towards the molecular aspects of *Bacopa monnieri* on neurological diseases.

5. Abbreviation

BME: *Bacopa monnieri* extract
AD: Alzheimer's disease
ADHD: Attention Deficit Hyperactivity Disorder
TNF-α: Tumor necrosis factor
IL: Interleukin
MCI: mild cognitive impairment
CNS: Central Nervous System
Ach: Acetylcholine
AchE: Acetyl cholinesterase
DNA: Deoxyribonucleic acid
ANOVA: Analysis of variance
CPRS: Conner's Parent Rating Scale-3
GABA: Gamma amino butyric acid
Glu: Glutamate
5-HT: 5-Hydroxytyrosine
DA: Dopamine
SOD: Superoxide dismutase
CAT: catalase
GPx: glutathione peroxidase
GSH: glutathione
NF-kB: nuclear factor kappa light chain enhancer of activated B cells
βA: Beta amyloid
NRF-2: Nuclear factor erythroid 2-related factor 2
COX-2: Clycooxygenase
GFAP: Glial fibrillary acidic protein

6. Declarations

6.1 Ethics approval and consent to participate

'Not Applicable'

6.2 Consent for publication

'Not Applicable'

6.3 Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study

6.4 Competing interests

The author declare that she has no competing interest"

6.5 Funding

No funding was required for this paper.

6.6 Authors' contributions

The Author has read and approved the manuscript. The whole paper was written by one author.

7. Acknowledgements

I would like to thank my Institution 'Sunandan Divatia School of Science, NMIMS (Deemed-to-be) University' for giving me this opportunity.

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